

The Role of Left Atrial Function in Diastolic Heart Failure

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New heart failure affects 500 000 Americans yearly. Nearly 50% of these patients have a normal left ventricular ejection fraction (LVEF) or so-called diastolic heart failure (DHF). New onset symptomatic DHF is a lethal disease with a 5-year mortality that approaches 50%.¹ Echo-Doppler techniques use LV filling patterns and tissue Doppler imaging of the mitral annulus to help identify and classify the degree of LV diastolic dysfunction, but work best in symptomatic patients with advanced disease.² Therefore, the diagnosis of early diastolic dysfunction, when asymptomatic and most treatable, remains problematic. A detailed causality-based, mechanistic understanding of what causes DHF, and how to most easily detect it, remains one of the most important unsolved problems in cardiovascular physiology and clinical cardiology.³

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Segmental LV deformation analysis for calculating contractile parameters such as strain and strain rate is now possible using noninvasive echo-Doppler techniques.² It has been reported that LA systolic and diastolic function can also be assessed using these Doppler strain techniques.⁴⁻⁶ Although LA enlargement increases with the severity of diastolic dysfunction,⁷ the ability of LA volume measurements to discriminate asymptomatic LV diastolic dysfunction from early DHF heart failure has not been possible. However, the concept that an alteration in LA function or stiffness may indicate this change is appealing.

The Present Study

To that end in this issue Kurt et al⁸ seek to advance our knowledge of additional clinical, anatomic and physiological correlates of DHF, with a particular focus on LA “diastolic function” and LA stiffness. They report clinical and echo-Doppler data on 64 subjects undergoing right heart catheterization with simultaneous echocardiography, and a control group of 27 control subjects. The 64 subjects included 25 with systolic heart failure (LVEF<50%), 20 with DHF and normal LVEF and 19 with LV hypertrophy from hypertension, also with normal LVEF but with no history of DHF. In

addition to LV mass and LA volumes they measured LA strain and strain rate during LV systole (LA_S) and LA contraction (LA_A), invasive LA stiffness (pulmonary wedge pressure/LA strain) and noninvasive stiffness as estimated by (E/e′)/(LA strain). Their main finding was that although asymptomatic hypertension patients with LVH and patients with normal LVEF and DHF had no differences in LV mass, LA volumes, or LA contractile function, DHF patients did have reduced LA strain and strain rate during LV systole, and an increased LA stiffness index. The analysis included use of receiver operating characteristic curves, and was adequately powered.

There is much to be commended in this effort. The incorporation of hemodynamic data are increasingly rare in clinical studies and cannot be adequately replaced by surrogates such as Doppler E/e′ ratios. The use of cardiac filling pressures with indices of LA function (strain and strain rate) to calculate LA stiffness is novel and worth exploring. The finding of similar increases in LA volume in patients with normal LVEF and diastolic dysfunction who had markedly different mean LA pressure is intriguing, goes against conventional wisdom and merits further investigation; although a detailed explanation of the methods used for LA volume should always be provided. Data which would have been helpful includes conventional mitral and pulmonary venous flow velocity variables. In addition, as seen in Figure 2, correlations and ROC curves do not always translate into clinical usefulness as a LA stiffness of 2 mm Hg, even if accurate, was associated with a PA systolic pressure range of 25 to 55 mm Hg.

In a larger sense the work Kurt et al⁸ points out the problem we, as investigators, have of trying to solve an important clinical issue by studying a single part (in this case the left atrium) of an integrated cardiovascular system in which the actions of all parts are coupled and affect each other. To fully understand the observations in the present work and help plan future research, it may be helpful to step back, consider how the entire heart works as it fills, and review the kinematic relationships between the left atrium and left ventricle that have already been established.

The Constant Volume Heart

The normal 4-chambered heart (the contents of the pericardial sac) is, within about 5%, a constant volume pump throughout the cardiac cycle⁹ that is anchored posteriorly in the area of the pulmonary veins, and anteriorly by the junction of the sternum and the diaphragm. The long axis dimension (from apex to pulmonary veins) of the 4-chambered heart remains fixed throughout the cardiac cycle (see accompanying MRI cine loop of the normal heart in 4-chamber [Movie 1] and parasternal long axis views [Movie 2]). A small 5% deficit in volume occurs in systole as a result

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of slight radial displacement (crescent effect) of the epicardial surface¹⁰ and is replenished by filling in early diastole as represented by the pulmonary vein D-wave.¹¹ This replenishment generates the conduit volume of the left atrium.¹² In contrast to the epicardial surface, the endocardium in systole undergoes significant radial displacement and the mitral and tricuspid annuli descend. This stretches both atria so that atrial and ventricular volumes reciprocate whereas total cardiac volume remains nearly constant (see Movie 1). Clearly, in systole the ventricles are the energy source and the atria the recipient of this work. This is also true in early diastole when ventricular relaxation and elastic recoil results in rapid ventricular filling (Doppler E-wave), movement of the mitral and tricuspid annuli upward and return of the atrial walls to their diastatic (equilibrium) state with a smaller volume. Only during the concluding portion of ventricular diastole, when atrial systole generates the Doppler A-wave, is the atrium an active energy source contracting and pulling the ventricles upward. All of the above kinematic relations can be easily appreciated by examination of cardiac MRI cine loops of normal adult hearts obtained in the usual, 4-chamber, parasternal long-axis, and short axis views (see Movies 1 and 2).

If the left ventricle is a large energy source, and the left atrium a small one that acts only briefly, and both chambers (but largely the ventricle) are constantly affecting the behavior of each other in a reciprocal fashion, is there a good time to study inherent atrial properties? Yes, most logically it would be during diastasis. There is no transmitral flow, there is no wall motion, and the atrium and the ventricle form a single chamber at the same pressure and at a fixed volume (see left ventricular angiogram, Movie 3). Diastasis defines the LV equilibrium volume,¹³ and by the constant volume property, it defines the equilibrium volume for the left atrium as well. To clarify, during diastasis, all forces are balanced (but not zero) so there is no wall motion and no transmitral flow. Hence the diastatic pressure-volume (P-V) relation can be differentiated from the end-diastolic P-V relation, which is conventionally used to determine LV stiffness.¹⁴

With the earlier discussion as background, and emphasizing that during the cardiac cycle the left heart generates external work (energy source) versus being the recipient of work (energy sink) let us examine the indexes used to characterize LA function—particularly LA diastolic function and dysfunction.

Left Atrial Ejection Fraction

LA ejection fraction is defined as $([LA \text{ pre-A Volume}] - [\text{minimum LA volume}]) / \text{pre-A volume}$. LA pre-A volume is the volume of the atrium at diastasis, when the ventricle is also at its equilibrium volume. In light of the (near) constant volume attribute of the heart, diastatic atrial volume is determined by 4-chamber interactions. However, among all the variables considered for LA function characterization, this static measure of volume is the one least confounded by other dynamic variables. Minimum LA volume at the end of the A-wave is determined by a combination of intrinsic LA contractility, and the load the contracting atrial myocardium faces. This load consists of passive LV properties (and 4-chamber heart coupling) and pulmonary

capacitance since retrograde flow occurs backward into the pulmonary veins. As can be surmised, each term in the algebraic expression for LAEF is confounded by these numerous variables.

LA Strain and Strain Rate

These measurements by echo-Doppler technique are provided in units of % strain or % strain/second. The definition of strain is change in length per unit length; strain rate is the temporal derivative of strain. These measurements are usually obtained during ventricular and atrial systole using sample volumes placed in the atrial myocardium near but clearly superior to the mitral annulus. For LA “diastolic” strain variables (during LV systole) the source of the strain is the ventricle doing external work on the atrium as the LV ejects blood into the aorta. The amount and rate of strain measured is determined primarily by ventricular and LV afterload attributes, although it follows that passive atrial tissue properties—on which the LV is also doing work, also play a role. That LA strain in early diastole must be strongly influenced by LV systolic function is in accordance with the constant volume requirement that atrial and ventricular volumes simultaneously reciprocate. This physiologic principle is underscored in the current work by Kurt et al⁸ by the observation that: “LV stroke volume was significantly related to LA_S strain, such that patients with higher LA_S strain exhibited higher stroke volumes ($r=0.35$, $P=0.04$).”

LA strain with LA contraction is a measure of LA systolic function relative to the load the LA faces as it pulls the mitral annulus upward and distends the LV while it simultaneously generates retrograde flow into the pulmonary veins. As discussed with LAEF it is confounded by both LV and pulmonary properties.

Hemodynamic Measurements

Pulmonary wedge pressure is an estimate of phase lagged LA pressure, in the presence of normal pulmonary vascular resistance. Viewing pulmonary wedge pressure as a time averaged (and slightly offset) analogue of mean LA pressure is appropriate. The factors that determine mean LAP (assuming all valves are normal) are multiple and include volume status, LV systolic and diastolic function, as well as preload and afterload. Hence, pulmonary wedge pressure is only partially determined by intrinsic LA function.

LA Stiffness

Stiffness is conventionally defined as the force required to displace a passive spring a unit length. Physiologically it is the change in pressure required to increase the volume of a passive container a unit amount. The units of strain in physiology are mm Hg/mL. In the current study “the ratio of pulmonary wedge pressure to LA systolic strain was used to estimate LA stiffness.” LA systolic strain was determined by averaging values from four sites in the LA myocardium. This measure of LA stiffness has units of mm Hg, rather than mm Hg/mL. Although this does not have the units of conventional stiffness it is a reasonable analogue. Importantly, the denominator in this expression, although measured in the LA wall, is determined primarily by longitudinal,

apically directed displacement of the mitral annulus by the contracting ventricle, whereas the posterior aspect of the LA remains fixed. (Recall reciprocation of LA/LV volumes required by constant volume attribute—see 4-chamber MRI cine loops). Hence this index, usually attributed to the LA as a stiffness measure, is very strongly influenced by LV properties. The noninvasive analog of LA stiffness as $[E/e']/LA_S$ was also reported. The fact that E/e' is related to LVEDP in the context of the constant volume heart has been derived from first principles¹⁵ and underscores the extent to which LV-LA coupling in diastole plays an important role.

To underscore the limitations of viewing LA strain during LV systole and LA stiffness as atrial properties—consider the physiologically symmetrical measurement of placing the Doppler sample volume for strain measurement in the LV wall, just below the mitral annulus during atrial systole. A peak strain and strain rate and stiffness for the LV can be measured but are clearly a consequence of atrial systole pulling up on the mitral annulus and ventricular myocardium. Labeling the obtained values as “LV diastolic function indexes,” because they occur during LV diastole, when they are caused by the work of LA systole, has obvious limitations.

Concluding Remarks

The primary energy source, the left ventricle, plays a central role in the various static and dynamic relationships between the left atrium and left ventricle, and hence will markedly influence any parameters used to characterize LA function. Thus, caution is appropriate about the extent to which the current study “examine(d) the contribution of LA diastolic dysfunction to the development of DHF.” Rather, the data presented further implicate the LV as a key determinant of the factors that lead to DHF with preserved LVEF. Nevertheless, the authors are to be commended for their consideration of LA diastolic function as a possible etiologic determinant of DHF, their selection of groups, the use of simultaneous echocardiography and catheterization data and their use of newer indices such as LA strain and LA stiffness.

Because of its increasing clinical importance DHF in patients with normal LVEF will remain a field of intense scrutiny and clinical relevance. Further advances in the use of noninvasive imaging (echocardiography, cardiac MRI, cine-CT) complemented by modeling of atrial-ventricular coupling in the context of the constant-volume attribute may help identify intrinsic LA properties that may be contributors to the development of DHF. It is also conceivable that as computer models of LV, 2-chamber and 4-chamber heart function become more tractable^{16–19} new physiological relations will be found that more fully characterize the role of intrinsic LA function in DHF. Ultimately, imaging and modeling in synergy, which includes the arterial system,²⁰ will lead to earlier diagnosis of DHF and implementation of therapy. Although skeptics remain whether diastolic function is the primary disorder in DHF,²¹ and the role of atrial remodeling and dysfunction has been considered,²² continued investigation at the cellular and molecular level will help determine the ultimate causes of changes in LV structure and function that result in DHF.³

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Disclosures

None.

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Supplemental Data

Movie 1: MRI cine loop of the normal heart in 4-chamber

Movies 2 and 3: Parasternal long axis views